CHAPTER III

RESULTS

1. Properties of Dipyrone Tablets (Formula 1 to Formula 30)

1.1 Weight Variation of Tablets

The average weight, standard deviation, and the coefficient of variation of tablets weight are shown in Tables 14 and 15. Each formula of dipyrone tablets possessed the weight variation in the limit of USP standard[3].

1.2 Hardness of Tablets

Tables 16 and 17 showed the hardness of dipyrone tablets. Each formula, the hardness of tablets was found to be about 5-6 kg. and 9-10 kg., except formula 7. The maximum hardness achieved in formula 7 was 8.72 kg.

1.3 Friability of Tablets

The results of the friability of tablets are shown in Tables 16 and 17. At the hardness of tablets 5-6 kg., the friability of tablets are ranged between 0.44% and 1.20%. Formulas 2 and 3, the friability of tablets were higher than the level of acceptibility. When the hardness of tablets were about 9-10 kg., the friability of tablets were decreased and ranged between 0.21% and 0.99%. Formula 2 also gave the tablets with the highest friability. The tablets

prepared from formula 6 (tablet hardness 9-10 kg.) were capping during the friability test.

1.4 Percent Labeled Amount of Tablets

The precent labeled amount of dipyrone tablets are shown in Tables 14 and 15.

1.5 Disintegration Time of Tablets

The disintegration time of tablets in 0.1 N HCl are shown in Table 8.

The effects of four tablet disintegrants : corn starch (I), sodium alginate (II), sodium carboxymethylcellulose (III), and sodium starch glycolate (IV), on disintegration time of tablets have been studied. There was slightly difference in the disintegration time of tablets.

Formula 1 to 5, the tablets containing corn starch as diluent and granulating with corn starch paste, at the hardness of tablets 5-6 kg., the disintegration time of tablets were ranked as follow : II > I > III > IV. It was noted that the disintegration time of the tablets containing disintegrant II was higher than the controlled tablets that had non-disintegrant. When the hardness of tablets changed to 9-10 kg., the disintegration time of tablet were increased. The disintegration time of tablets were ranked as follow : II > III > IV > I. The disintegration time of tablets containing disintegrants II and III were higher than the controlled tablets.

Formula 6 to 10, the tablets contained corn starch as diluent and granulated with polyvinylpyrrolidone. At the hardness of tablets

Table 8 Disintegration Time of Dipyrone Tablet (Formula 1-30).

Formula	Disintegration Time, min. ± S.D.	
	Tablet Hardness 5-6 kg.	Tablet Hardness 9-10 kg.
1	6.50 ± 0.09	6.85 ± 0.12
2	6.53 ± 0.15	6.69 ± 0.10
3	7.11 ± 0.29	7.85 ± 0.24
4	6.42 ± 0.20	7.17 ± 0.17
5	6.29 ± 0.09	6.82 ± 0.08
6	5.17 ± 0.15	5.17 ± 0.10
7	4.88 ± 0.10	4.90 ± 0.10
8	5.22 ± 0.17	5.71 ± 0.07
9	5.11 ± 0.09	5.74 ± 0.13
10	4.93 ± 0.08	5.22 ± 0.07
11	5.15 ± 0.13	5.50 ± 0.14
12	4.94 ± 0.14	5.56 ± 0.16
13	5.57 ± 0.18	6.15 ± 0.08
14	5.71 ± 0.16	5.97 ± 0.07
15	5.06 ± 0.11	5.21 ± 0.07

Table 8 (Continue) Disintegration Time of Dipyrone Tablet (Formula 1-30).

Formula	Disintegration Time, min. ± S.D.	
	Tablet Hardness 5-6 kg.	Tablet Hardness 9-10 kg.
16	6.51 ± 0.08	6.68 ± 0.12
17	6.71 ± 0.17	7.54 ± 0.16
18	7.30 ± 0.11	7.92 ± 0.10
19	6.76 ± 0.11	7.38 ± 0.14
20	6.64 ± 0.09	7.11 ± 0.07
21	5.24 ± 0.06	5.47 ± 0.10
22	5.76 ± 0.16	5.99 ± 0.12
23	5.61 ± 0.16	6.28 ± 0.16
24	5.76 ± 0.10	6.43 ± 0.10
25	5.25 ± 0.05	5.36 ± 0.04
26	6.24 ± 0.19	6.25 ± 0.22
27	6.29 ± 0.33	6.49 ± 0.16
28	6.15 ± 0.16	6.90 ± 0.15
29	6.19 ± 0.14	6.36 ± 0.14
30	5.60 ± 0.12	5.76 ± 0.03

5-6 kg., the disintegration time of tablets were ranked as follow : II > III > IV > I. Disintegrant II was increased the disintegration time of tablets in stead of decreasing the disintegration time. When the hardness of tablets changed to 9-10 kg., the disintegration time of tablets were increased except the controlled tablets. The disintegration time of tablets containing the disintegrants except disintegrant I were higher than the controlled tablets. But the tablets containing disintegrant I, the maximum hardness of tablets was only 8.72 kg.

Formula 11 to 15, the tablets contained corn starch as diluent and granulated with gelatin. At the hardness of tablets 5-6 kg., the disintegration time of tablets were ranked as follow : III > II > IV > I. The disintegration time of tablets containing disintegrants II and III were higher than the controlled tablets. When the hardness of tablets changed to 9-10 kg., the disintegration time of tablets were increased and ranked as follow : II > III > I > IV. The tablets containing disintegrant IV had the disintegration time lower than the controlled tablets. While the other disintegrants were increased the disintegration time in stead of decreasing the disintegration time.

Formula 16 to 20, the tablets contained lactose as diluent and granulated with corn starch paste. An increase in the hardness of tablets caused an increase in the disintegration time of tablets. At two levels of the hardness of tablets, the four tablet disintegrants increased the disintegration time in stead of decreasing when compared

with the controlled tablets.

Formula 21 to 25, the tablets contained lactose as diluent and granulated with polyvinylpyrrolidone. At the hardness of tablets 5-6 kg., the disintegration time of tablets containing four different tablet disintegrants were higher than the controlled tablets. When the hardness of tablets changed to 9-10 kg., the disintegration time of tablets were increased. Disintegrant IV was the only disintegrant that decreased the disintegration time of tablets while the other disintegrants were not.

Formula 26 to 30, the tablets contained lactose as diluent and granulated wiht gelatin. At the hardness of tablets 5-6 kg., the disintegration time of tablets were ranked as follow : I > III > II > IV. The disintegration time of tablets containing disintegrant I was higher than the controlled tablets. When the hardness of tablets changed to 9-10 kg., the disintegration time of tablets were increased. Disintegrant IV was the only disintegrant that decreased the disintegration time of tablets lower than the controlled tablets.

The effects of three binding agents : corn starch paste, polyvinylpyrrolidone, and gelatin, on the disintegration time of tablets have been studied. When compared among the tablets containing the same diluent and disintegrant but granulating with three different binders, the disintegration time of tablets were ranked as follow : corn starch paste > gelatin > polyvinylpyrrolidone.

The effects of diluents : corn starch and lactose, have been studied on the disintegration time of tablets. When compared between

the tablets containing the same disintegrant and granulating with the same binder, the disintegration time of tablets containing corn starch was slightly lower than the tablets containing lactose.

On the basis of the disintegration time of tablets, it may be concluded as the following : There were slightly differences in the disintegration time of dipyrone tablets prepared from various formulations. Therefore, the disintegration time of tablets can not be used to differentiate among those formulations employed. However, corn starch was considered slightly better than lactose when used as diluent. Polyvinylpyrrolidone found to be better than gelatin and corn starch paste. Among four tablet disintegrants, sodium starch glycolate and corn starch were considered satisfactory disintegrants.

The tablets containing corn starch as diluent, sodium starch glycolate as disintegrant and polyvinylpyrrolidone as binder; Formula 10 (tablet hardness 5-6 kg.), had the lowest disintegration time (4.93 ± 0.08 minutes).

An increase in the hardness of tablets, the disintegration time of tablets increased.

1.6 Dissolution Time of Tablets

The dissolution time of tablets that used as a comparative parameter in the differentiation of dipyrone tablet formulations in this study was the time required for 90% of dipyrone to dissolve and read from the dissolution profiles. The results that showed in Table 9 were the mean of four determinations.

Table 9 Dissolution Time ($t_{90\%}$) of Dipyrone Tablet (Formula 1-30).

Formula	Dissolution Time ($t_{90\%}$), min. ± S.D.	
	Tablet Hardness 5-6 kg.	Tablet Hardness 9-10 kg.
1	48.09 ± 4.02	74.69 ± 4.77
2	28.85 ± 3.45	41.99 ± 5.26
3	41.55 ± 3.00	59.86 ± 4.70
4	24.09 ± 3.81	32.02 ± 1.54
5	31.80 ± 1.69	43.80 ± 4.70
6	18.46 ± 1.15	20.64 ± 1.41
7	16.31 ± 2.23	13.06 ± 0.99
8	18.20 ± 2.53	22.32 ± 2.01
9	12.05 ± 1.35	13.92 ± 0.48
10	13.22 ± 2.39	13.56 ± 1.39
11	29.95 ± 1.36	33.44 ± 3.24
12	13.91 ± 0.96	22.30 ± 4.42
13	18.37 ± 0.75	22.38 ± 2.48
14	12.84 ± 1.19	13.32 ± 0.37
15	14.08 ± 0.68	24.42 ± 3.17

Table 9 (Continue) Dissolution Time ($t_{90\%}$) of Dipyrone Tablet (Formula 1-30).

Formula	Dissolution Time ($t_{90\%}$), min. ± S.D.	
	Tablet Hardness 5-6 kg.	Tablet Hardness 9-10 kg.
16	45.16 ± 5.72	62.84 ± 5.17
17	46.40 ± 1.60	57.54 ± 1.10
18	43.24 ± 2.67	76.00 ± 9.19
19	26.05 ± 1.71	30.34 ± 3.40
20	29.54 ± 1.48	41.57 ± 2.84
21	22.29 ± 1.89	29.84 ± 3.73
22	17.75 ± 0.34	22.69 ± 1.42
23	18.42 ± 1.65	23.79 ± 0.65
24	13.26 ± 0.80	14.23 ± 1.13
25	16.51 ± 1.67	18.34 ± 0.58
26	31.65 ± 2.64	34.28 ± 3.84
27	19.73 ± 1.47	27.10 ± 1.77
28	16.16 ± 1.17	18.00 ± 0.56
29	12.71 ± 0.66	16.66 ± 0.99
30	21.47 ± 2.34	27.24 ± 2.97

1.6.1 The Effects of Disintegrating Agents on the Dissolution Time of Tablets

The effects of four tablet disintegrants : corn starch (I), sodium alginate (II), sodium carboxymethylcellulose (III), and sodium starch glycolate (IV), have been studied on the dissolution time ($t_{90\%}$) of dipyrone tablets.

Formula 1 to 5, there are distinct differences in the dissolution profiles of the tablets containing different types of disintegrants (Figs. 1 and 2). The dissolution time of tablets were ranked as follow : II > IV > I > III. An increase in the hardness of tablets, the dissolution time of tablets increased. At two levels of the hardness of tablets, the effects of four tablet disintegrants on the dissolution time of tablets were significant at 5% level ($F_{3,12,0.05} = 3.49$, $F_{ratio} = 22.68$ and 28.58, respectively). Test significant difference between each pair of disintegrants by using Duncan's New Multiple Range Test, the results indicated that there were significant differences. Among the four tablet disintegrants, the disintegrant III was found to be the best.

Formula 6 to 10, at the hardness of tablets 5-6 kg., the dissolution time and dissolution profiles of the tablets are shown in Table 9 and Fig. 3, repectively. The dissolution time of tablets were ranked as follow : II > I > IV > III. The effects of four tablet disintegrants on the dissolution time of tablets were significant at 5% level ($F_{3,12,0.05} = 3.49$, $F_{ratio} = 6.73$). By using Duncan's New Multiple Range Test, each pair of disintegrants

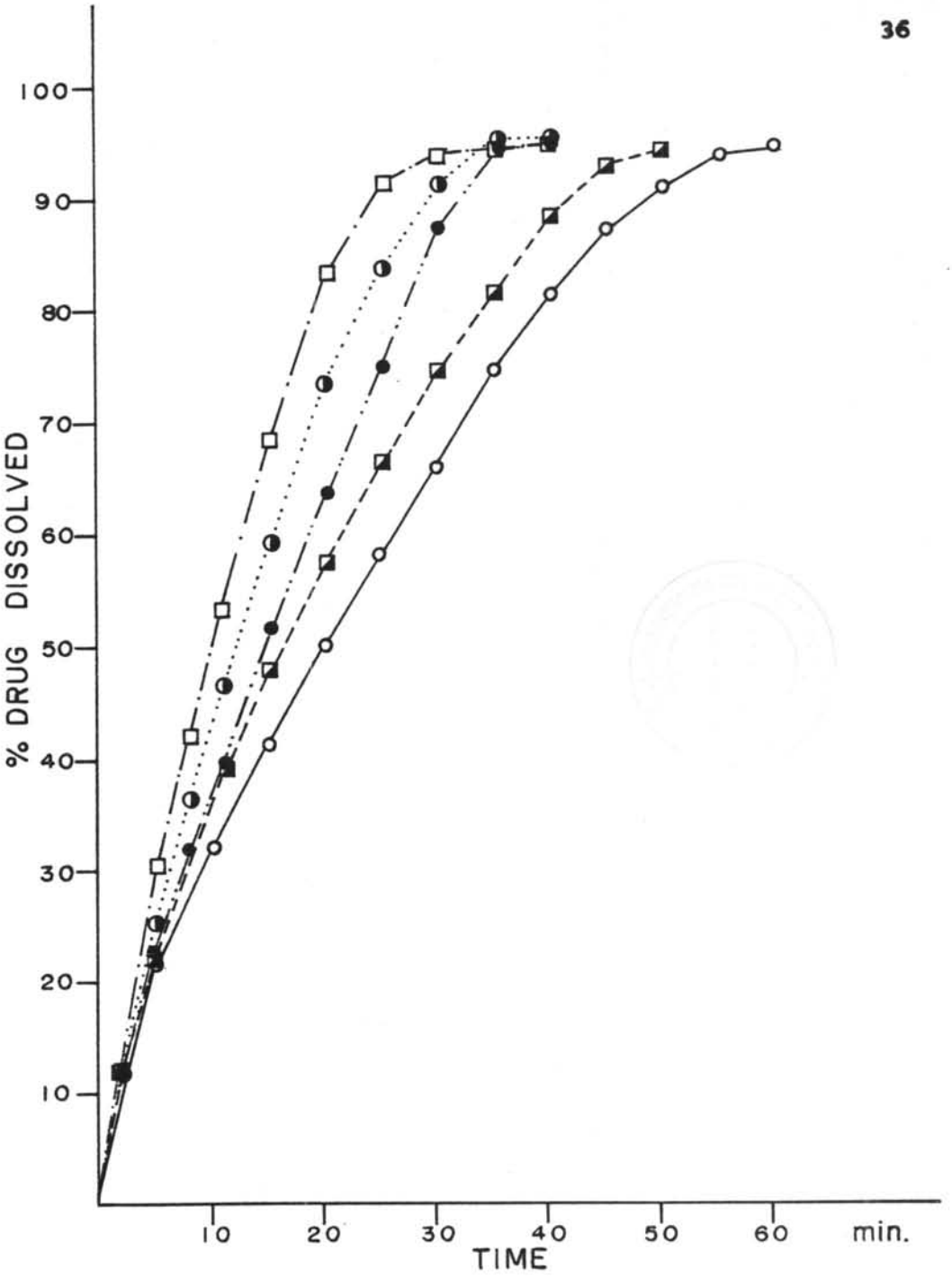

Figure 1 Dissolution Profiles of Dipyrone Tablets, Formula 1-5, Hardness 5-6 kg. (Each point on the curve is the mean value of 4 determinations.)

Key : —○— , Formula 1 (Non-disintegrant);

·····◑····· , Formula 2 (Corn Starch);

--◪-- , Formula 3 (Sodium Alginate);

-·-□-·- , Formula 4 (Sodium Carboxymethylcellulose);

-·-●-·- , Formula 5 (Sodium Starch Glycolate).

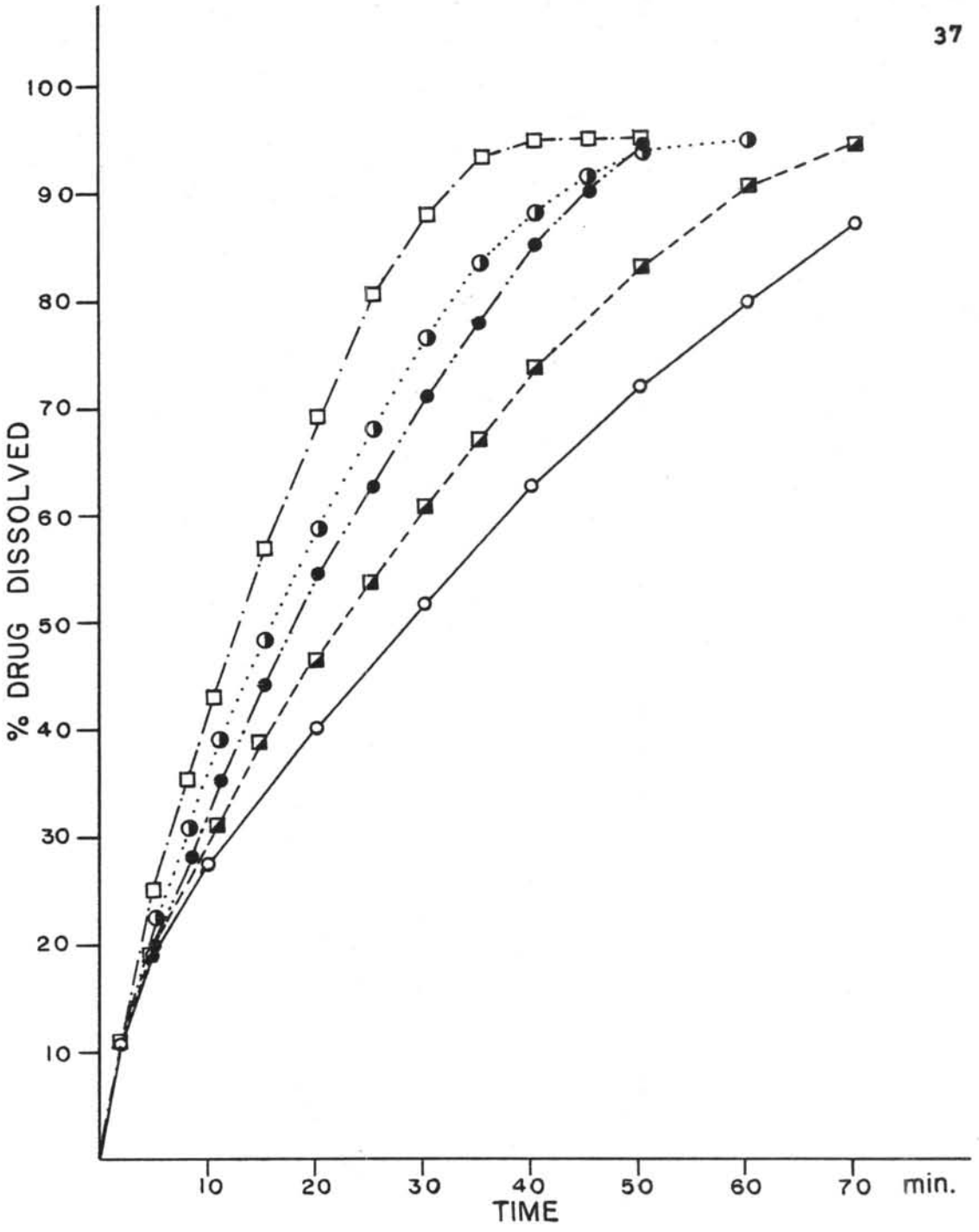

Figure 2 Dissolution Profiles of Dipyrone Tablets, Formula 1-5 Hardness 9-10 kg. (Each point on the curve is the mean value of 4 determinations.)

Key : —○— , Formula 1 (Non-disintegrant);

·····◑····· , Formula 2 (Corn Starch);

- - ◪ - - , Formula 3 (Sodium Alginate);

—·□·— , Formula 4 (Sodium Carboxymethylcellulose);

—·●·— , Formula 5 (Sodium Starch Glycolate).

was found significant difference except the disintegrants I and II, I and IV, III and IV. Although, the dissolution time of tablets containing disintegrants III or IV had non-significant difference. The tablets containing disintegrant III had the lowest dissolution time. When the hardness of tablets changed to 9-10 kg., the dissolution time of tablets were slightly increased except Formula 7. Formula 7, when the hardness of tablets increased, the dissolution time of tablets decreased. The dissolution time and dissolution profiles of the tablets are shown in Table 9 and Fig. 4, respectively. The dissolution time of tablets were ranked as follow : II > III > IV > I. Although, the tablets containing disintegrant I possessed the lowest dissolution time. The tablets required the highest compressional force to reach maximum hardness of tablets only 8.72 kg. So that, corn starch was not a satisfactory disintegrant in this case. Statistical analysis showed that there were significant differences among the dissolution time of tablets produced by the four tablet disintegrants ($F_{3,12,0.05} = 3.49$, $F_{ratio} = 43.43$). There were significant differences when the comparisons between disintegrants were made by using Duncan's New Multiple Range Test except the disintegrants I and III, I and IV, III and IV. Therefore, at two levels of the hardness of tablets, the disintegrants III and IV were considered satisfactory disintegrants.

Formula 11 to 15, at the hardness of tablets 5-6 kg., the dissolution time and dissolution profiles of the tablets are shown in Table 9 and Fig. 5, respectively. The dissolution of tablets

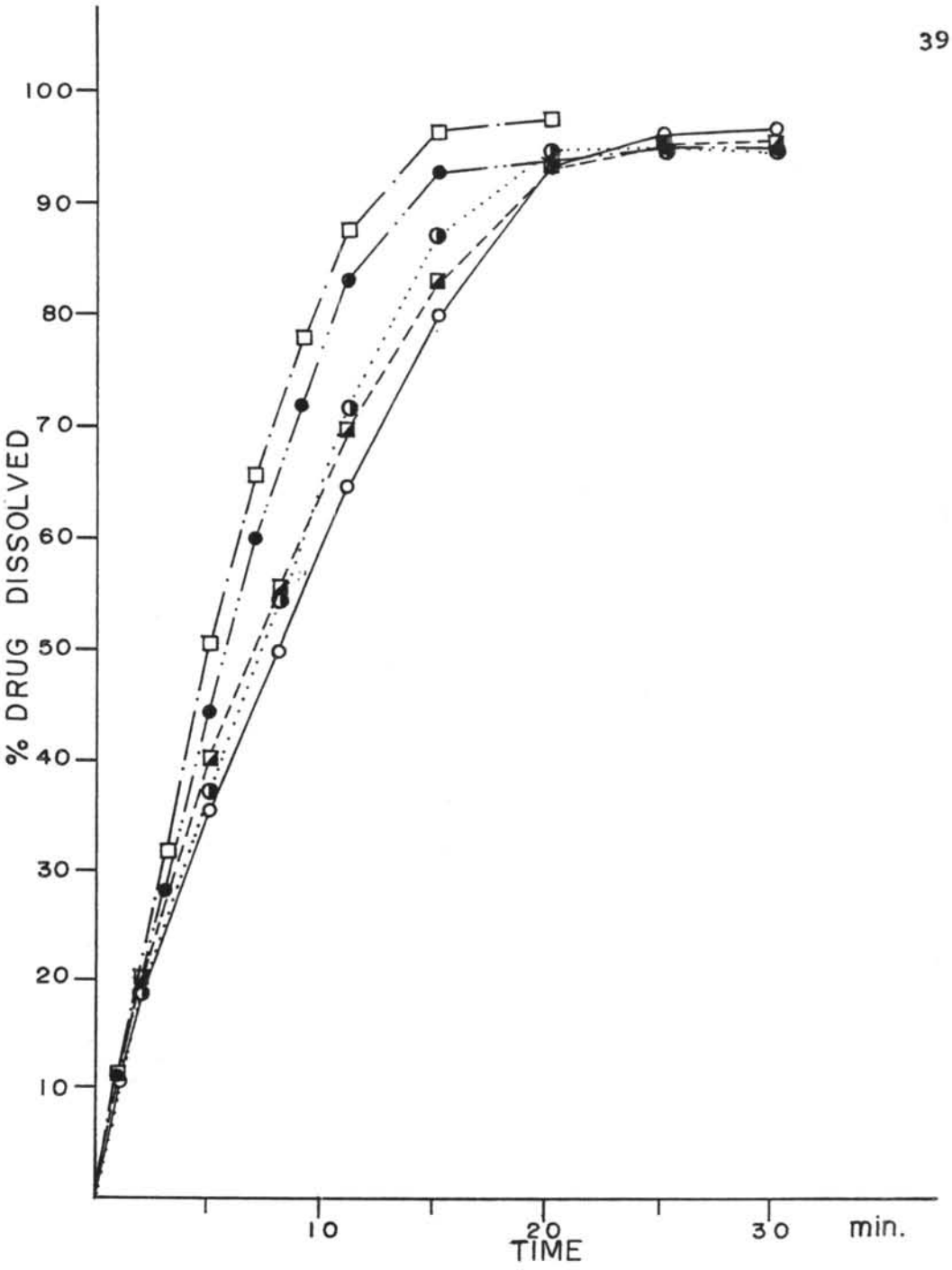

Figure 3 Dissolution Profiles of Dipyrone Tablets, Formula 6-10, Hardness 5-6 kg. (Each point on the curve is the mean value of 4 determinations.)

Key : —○— , Formula 6 (Non-disintegrant);

·····◑····· , Formula 7 (Corn Starch);

---◪--- , Formula 8 (Sodium Alginate);

-·-□-·- , Formula 9 (Sodium Carboxymethylcellulose);

-··-●-··- , Formula 10 (Sodium Starch Glycolate).

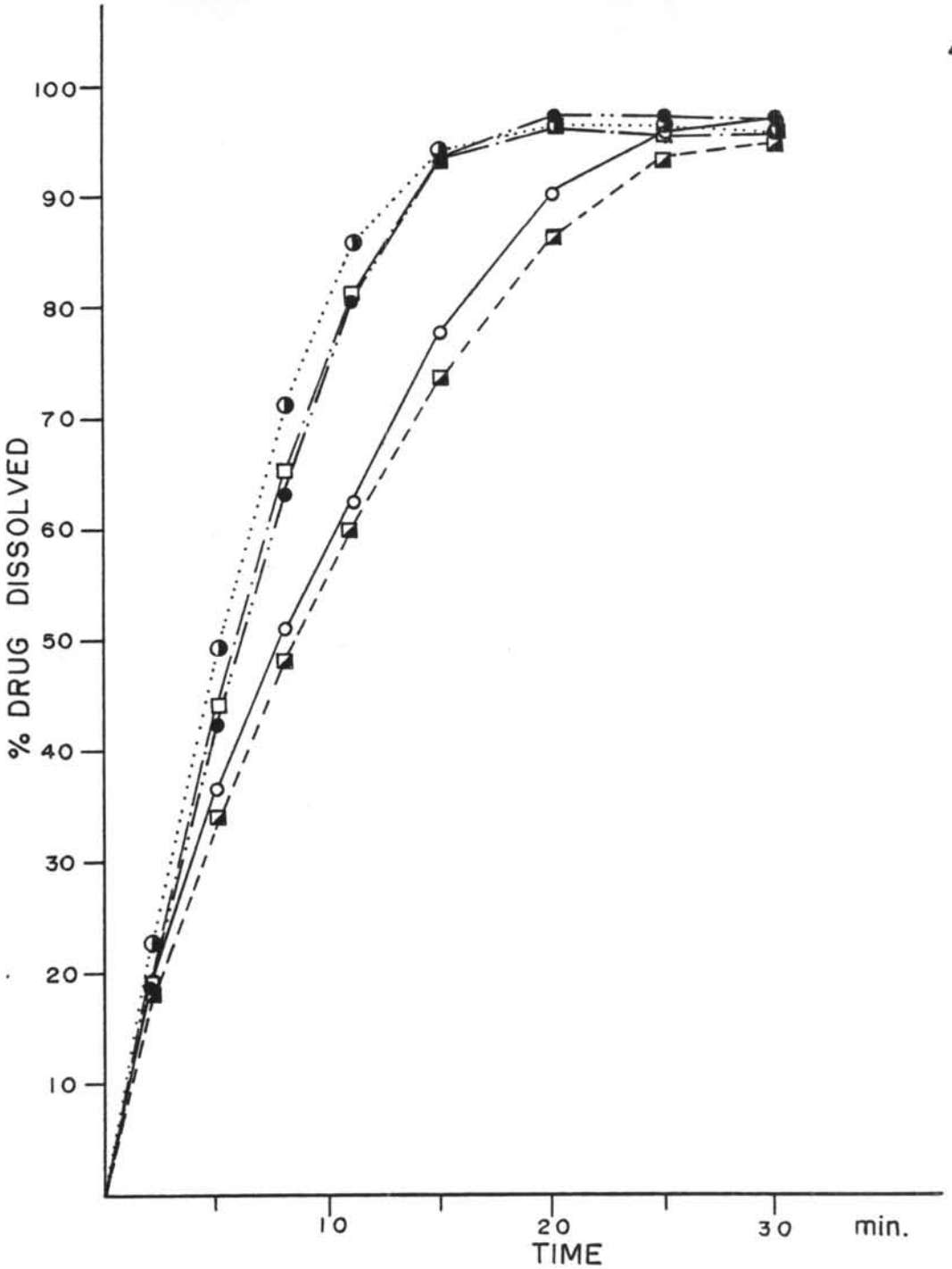

Figure 4 Dissolution Profiles of Dipyrone Tablets, Formula 6-10, Hardness 9-10 kg. (Each point on the curve is the mean value of 4 determinations.)

Key : —○— , Formula 6 (Non-disintegrant);

·····◑····· , Formula 7 (Corn Starch);

- - -◪- - - , Formula 8 (Sodium Alginate);

—·□·— , Formula 9 (Sodium Carboxymethylcellulose);

—··●··— , Formula 10 (Sodium Starch Glycolate).

were ranked as follow : II > I > IV > III. The effects of four tablet disintegrants on the dissolution time of tablets were significant at 5% level ($F_{3,12,0.05} = 3.49$, $F_{ratio} = 29.85$). By using Duncan's New Multiple Range Test, each pair of disintegrants was found significant difference except the disintegrants I and IV, I and III, III and IV. Therefore, the disintegrants I, III and IV were considered satisfactory disintegrants. Although, the tablets containing disintegrant III possessed the lowest dissolution time. When the hardness of tablets changed to 9-10 kg., the dissolution time of the tablets were increased. The dissolution time and dissolution profiles of the tablets are shown in Table 9 and Fig. 6, respectively. The dissolution time of tablets were ranked as follow : IV > II > I > III. The effects of four tablet disintegrants on the dissolution time of tablets were significant at 5% level ($F_{3,12,0.05} = 3.49$, $F_{ratio} = 10.96$). By using Duncan's New Multiple Range Test, the results showed that the disintegrants III and I, III and II, III and IV had significant differences. Therefore, the disintegrant III was considered satisfactory and found to be the best among four tablet disintegrants.

Formula 16 to 20, at the hardness of tablets 5-6 kg., the dissolution time and dissolution profiles of the tablets are shown in Table 9 and Fig. 7, respectively. The dissolution time of tablets were ranked as follow : I > II > IV > III. The effects of four tablet disintegrants on the dissolution time of tablets were significant at 5% level ($F_{3,12,0.05} = 3.49$, $F_{ratio} = 108.45$). The dissolution time of tablets containing disintegrant I was higher than

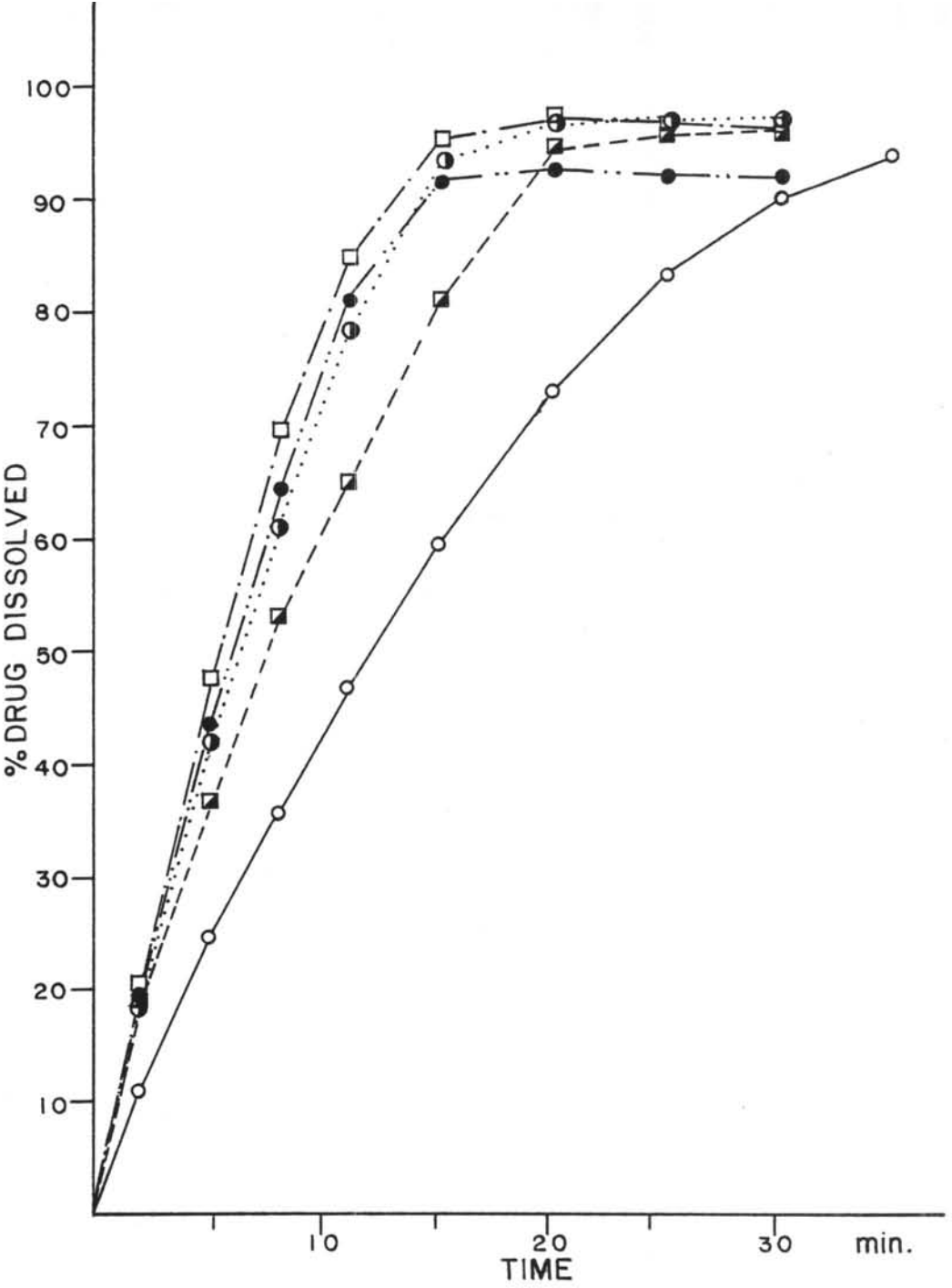

Figure 5 Dissolution Profiles of Dipyrone Tablets. Formula 11-15, Hardness 5-6 kg. (Each point on the curve is the mean value of 4 determinations.)

Key : —○— , Formula 11 (Non-disintegrant);

·····◑····· , Formula 12 (Corn Starch);

- - -◪- - - , Formula 13 (Sodium Alginate);

—·-□-·— , Formula 14 (Sodium Carboxymethylcellulose);

—·-●-·— , Formula 15 (Sodium Starch Glycolate).

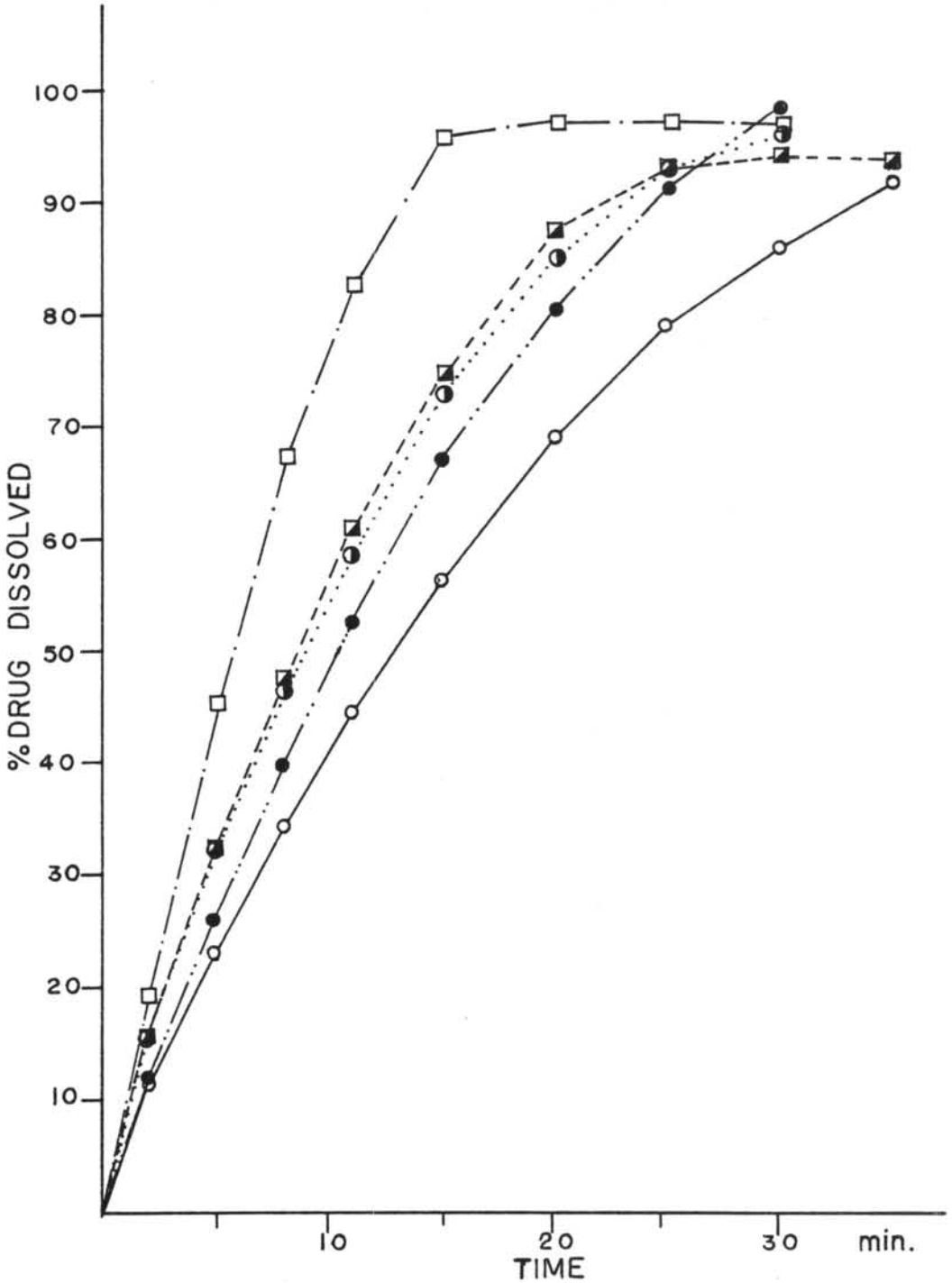

Figure 6 Dissolution Profiles of Dipyrone Tablets, Formula 11-15, Hardness 9-10 kg. (Each point on the curve is the mean value of 4 determinations.)

Key : —○— , Formula 11 (Non-disintegrant);

·····◑····· , Formula 12 (Corn Starch);

- - ◪ - - , Formula 13 (Sodium Alginate);

—·□·— , Formula 14 (Sodium Carboxymethylcellulose);

—·●·— , Formula 15 (Sodium Starch Glycolate).

the controlled tablets. When the disintegrants were compared between each other by using Duncan's New Multiple Range Test, the results showed that each pair of disintegrants had significant difference. When the hardness of tablets changed to 9-10 kg., the dissolution time of tablets were increased. The dissolution time and dissolution profiles of the tablets are shown in Table 9 and Fig. 8, respectively. The dissolution time of tablets were ranked as follow : II > I > IV > III. The effects of four tablet disintegrants on the dissolution time of tablets were significant at 5% level ($F_{3,12,0.05} = 3.49$, $F_{ratio} = 59.88$). When the disintegrants were compared between each other by using Duncan's New Multiple Range Test, the results showed that each pair of disintegrants had significant difference. Therefore, at two levels of the hardness of tablets, the disintegrant III was found to be the best among four tablet disintegrants.

Formula 21 to 25, at the hardness of tablets 5-6 kg., the dissolution time and dissolution profiles of the tablets are shown in Table 9 and Fig. 9, respectively. The dissolution time of tablets were ranked as follow : II > I > IV > III. The effects of four tablet disintegrants on the dissolution time of tablets were significant at 5% level ($F_{3,12,0.05} = 3.49$, $F_{ratio} = 13.42$). When the disintegrants were compared between each other by using Duncan's New Multiple Range Test, the results showed that the disintegrants III and I, III and II, III and IV had significant differences while the other pairs of disintegrants were not. When the hardness of tablets changed to 9-10 kg., the dissolution time of tablets were increased. The dissolution time and dissolution profiles of tablets are shown in Table 9

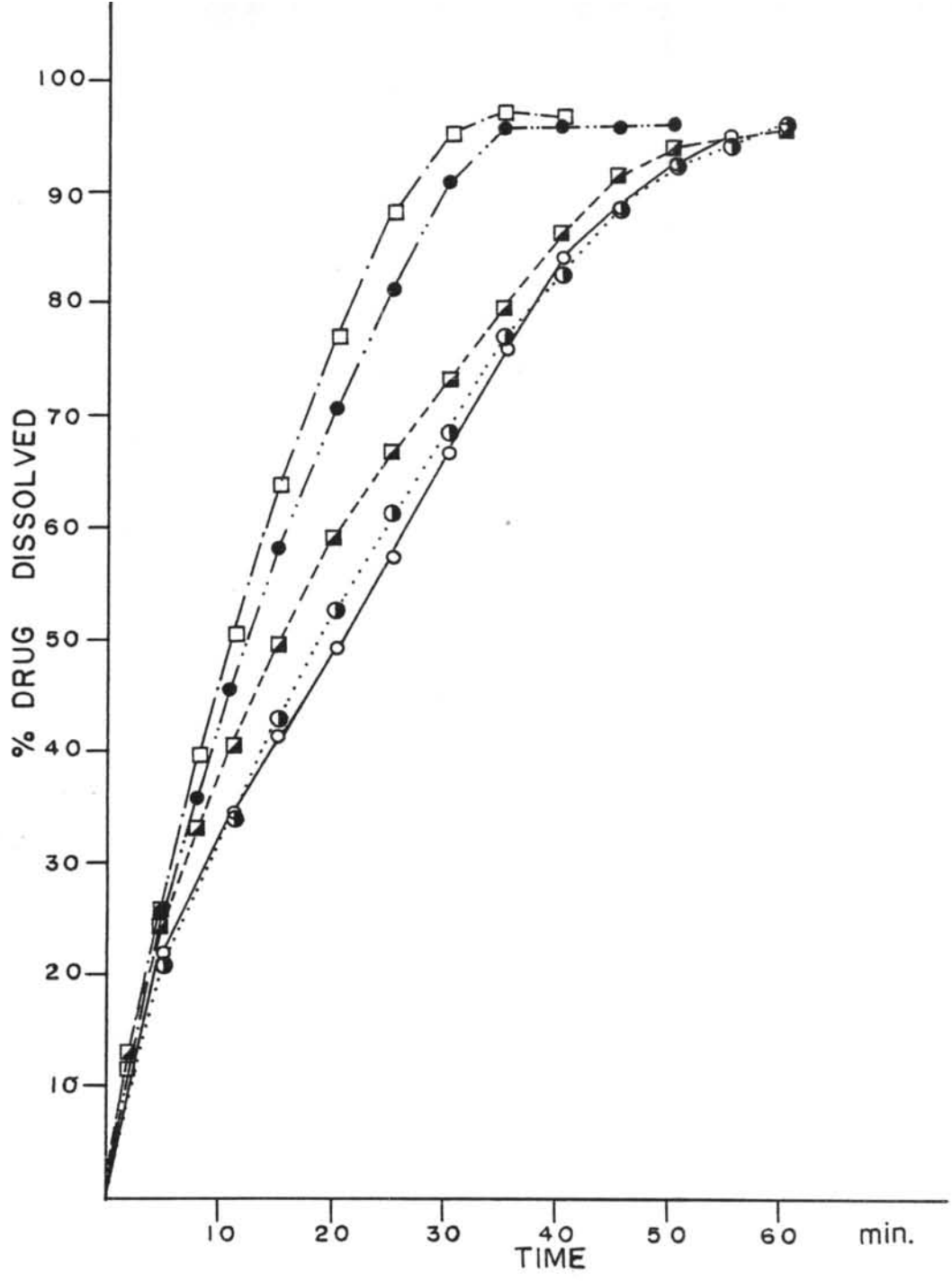

Figure 7 Dissolution Profiles of Dipyrone Tablets, Formula 16-20, Hardness 5-6 kg. (Each point on the curve is the mean value of 4 determinations.)

Key : —○— , Formula 16 (Non-disintegrant);

·····◑····· , Formula 17 (Corn Starch);

– –◪– – , Formula 18 (Sodium Alginate);

–·–□–·– , Formula 19 (Sodium Carboxymethylcellulose);

–·–●–·– , Formula 20 (Sodium Starch Glycolate).

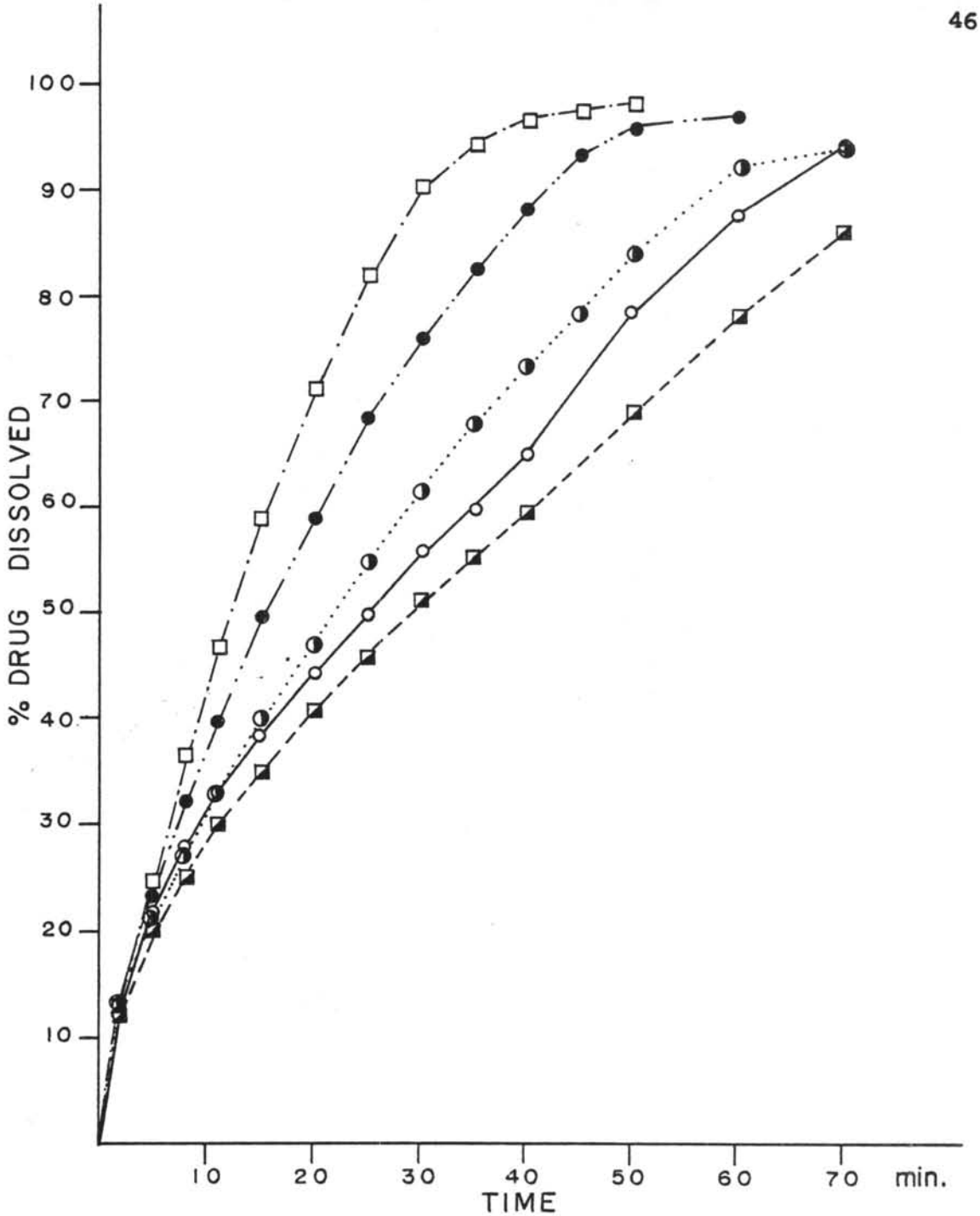

Figure 8 Dissolution Profiles of Dipyrone Tablets, Formula 16-20, Hardness 9-10 kg. (Each point on the curve is the mean value of 4 determinations.)

Key : —○— , Formula 16 (Non-disintegrant);

·····◑····· , Formula 17 (Corn Starch);

- - -◪- - - , Formula 18 (Sodium Alginate);

-·-□-·- , Formula 19 (Sodium Carboxymethylcellulose);

—·-●-·— , Formula 20 (Sodium Starch Glycolate).

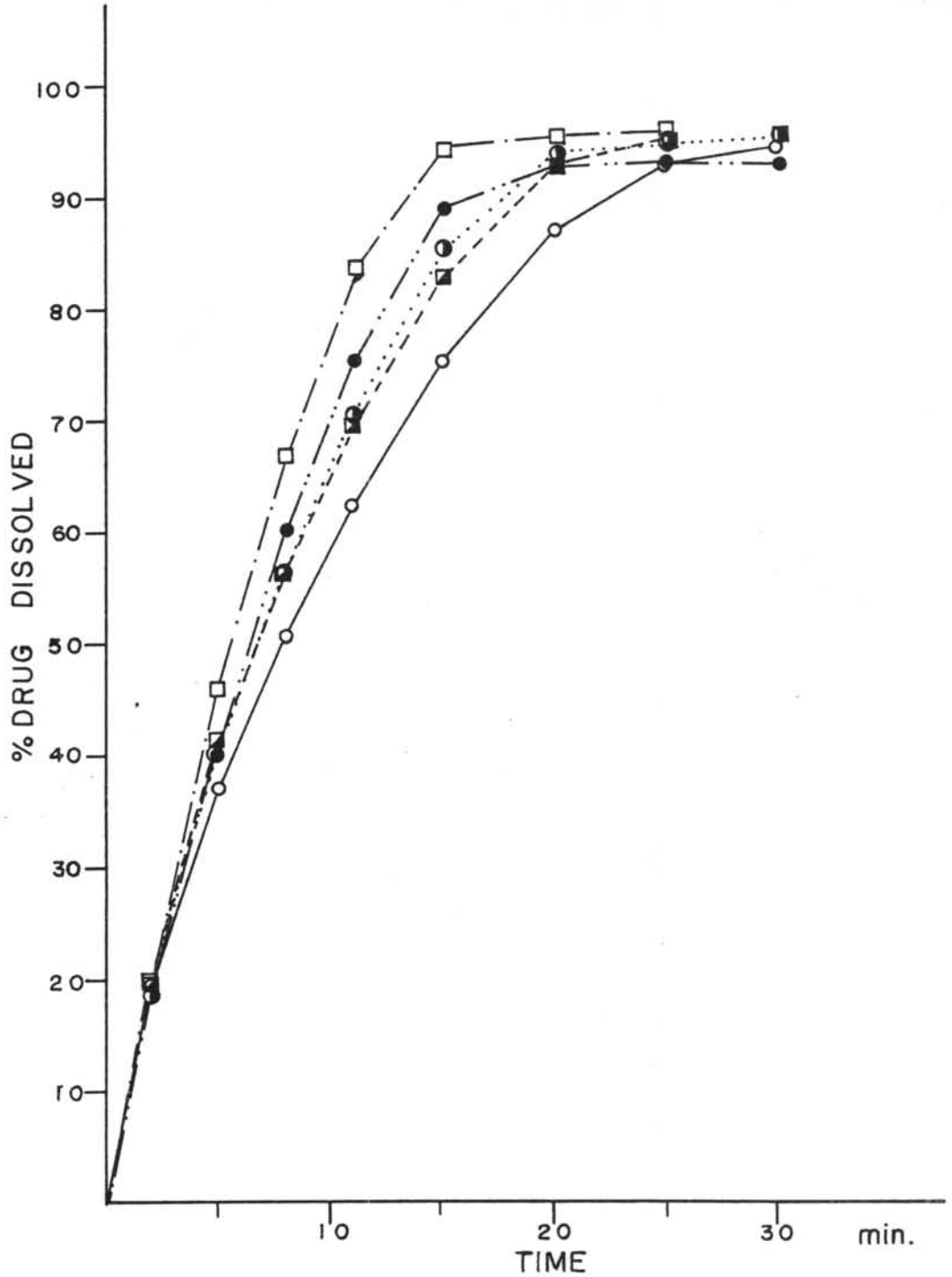

Figure 9 Dissolution Profiles of Dipyrone Tablets, Formula 21-25, Hardness 5-6 kg. (Each point on the curve is the mean value of 4 determinations.)

Key : —○— , Formula 21 (Non-disintegrant);

·····◑····· , Formula 22 (Corn Starch);

--◪-- , Formula 23 (Sodium Alginate);

—·□·— , Formula 24 (Sodium Carboxymethylcellulose);

—·●·— , Formula 25 (Sodium Starch Glycolate).

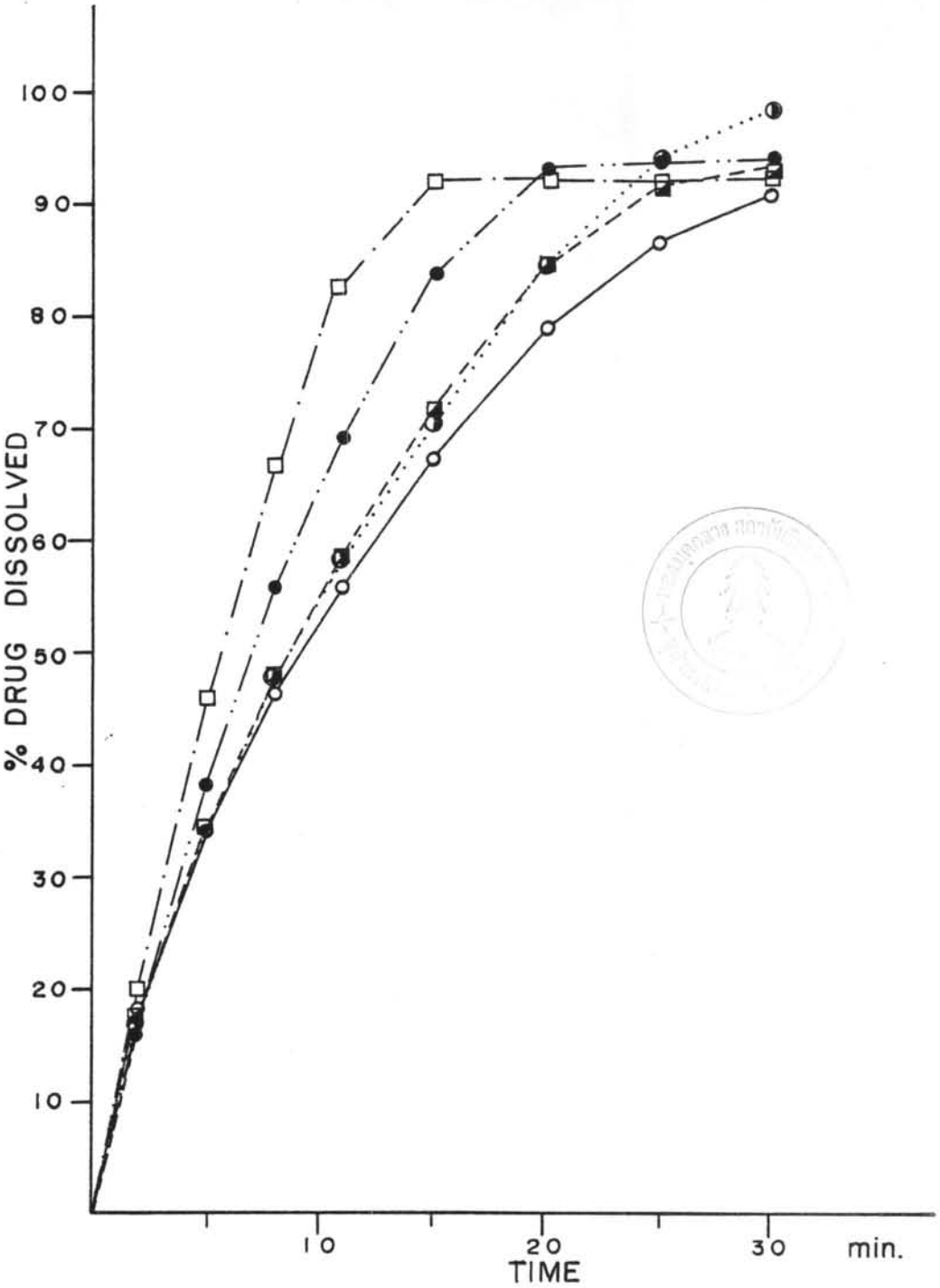

Figure 10 Dissolution Profiles of Dipyrone Tablets, Formula 21-25, Hardness 9-10 kg. (Each point on the curve is the mean value of 4 determinations).

Key : —○— , Formula 21 (Non-disintegrant);

·····◑····· , Formula 22 (Corn Starch);

- - -◪- - - , Formula 23 (Sodium Alginate);

-·-□-·- , Formula 24 (Sodium Carboxymethylcellulose);

-·-●-·- , Formula 25 (Sodium Starch Glycolate).

and Fig. 10, respectively. The dissolution time of tablets were ranked as follow : II > I > IV > III. The effects of four tablet disintegrants on the dissolution time of tablets were significant at 5% level ($F_{3,12,0.05} = 3.49$, $F_{ratio} = 75.48$). When the disintegrants were compared between each other by using Duncan's New Multiple Range Test, the results showed that each pair of disintegrants had significant difference; except the disintegrants I and II. Therefore, at two levels of the hardness of tablets, the disintegrant III was found to be the best among four tablet disintegrants.

Formula 26 to 30, at the hardness of tablets 5-6 kg., the dissolution time and dissolution profiles of tablets are shown in Table 9 and Fig. 11, respectively. The dissolution time of tablets were ranked as follow : IV > I > II > III. The effects of four tablet disintegrants on the dissolution time of tablets were significant at 5% level ($F_{3,12,0.05} = 3.49$, $F_{ratio} = 25.92$). When the disintegrants were compared between each other by using Duncan's New Multiple Range Test, the results showed that each pair of disintegrants had significant difference; except the disintegrants I and IV. When the hardness of tablets changed to 9-10 kg., the dissolution time of tablets were increased. The dissolution time and dissolution profiles of tablets are shown in Table 9 and Fig. 12, respectively. The dissolution time of tablets were ranked as follow : IV > I > II > III. The effects of four tablet disintegrants on the dissolution time of tablets were significant at 5% level ($F_{3,12,0.05} = 3.49$, $F_{ratio} = 39.22$). When the disintegrants were compared between each other, the results showed that each pair of disintegrants had significant difference,

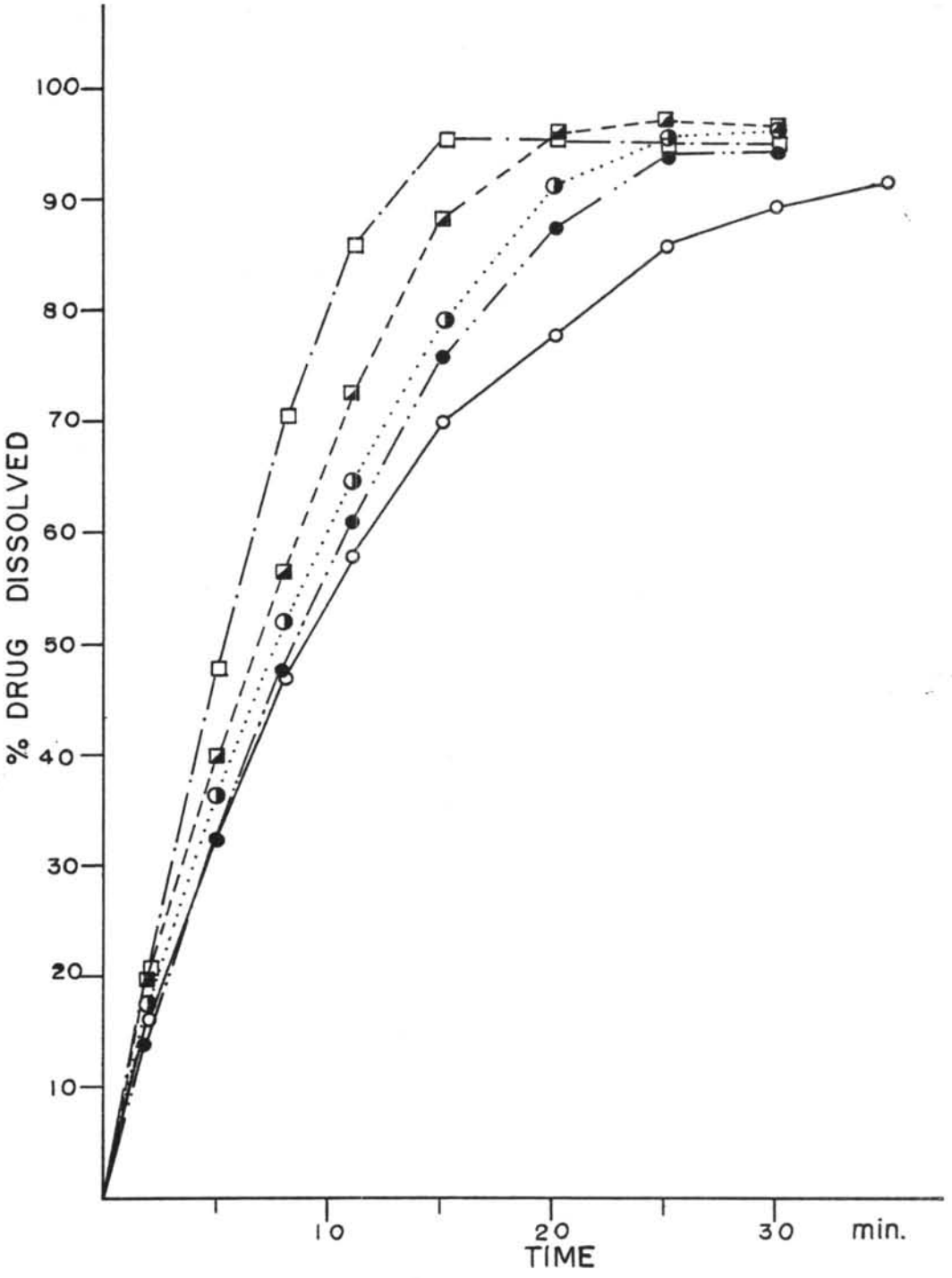

Figure 11 Dissolution Profiles of Dipyrone Tablets, Formula 26-30, Hardness 5-6 kg. (Each point on the curve is the mean value of 4 determinations.)

Key : —○— , Formula 26 (Non-disintegrant);

·····◑····· , Formula 27 (Corn Starch);

---◪--- , Formula 28 (Sodium Alginate);

—·□·— , Formula 29 (Sodium Carboxymethylcellulose);

—·●·— , Formula 30 (Sodium Starch Glycolate).

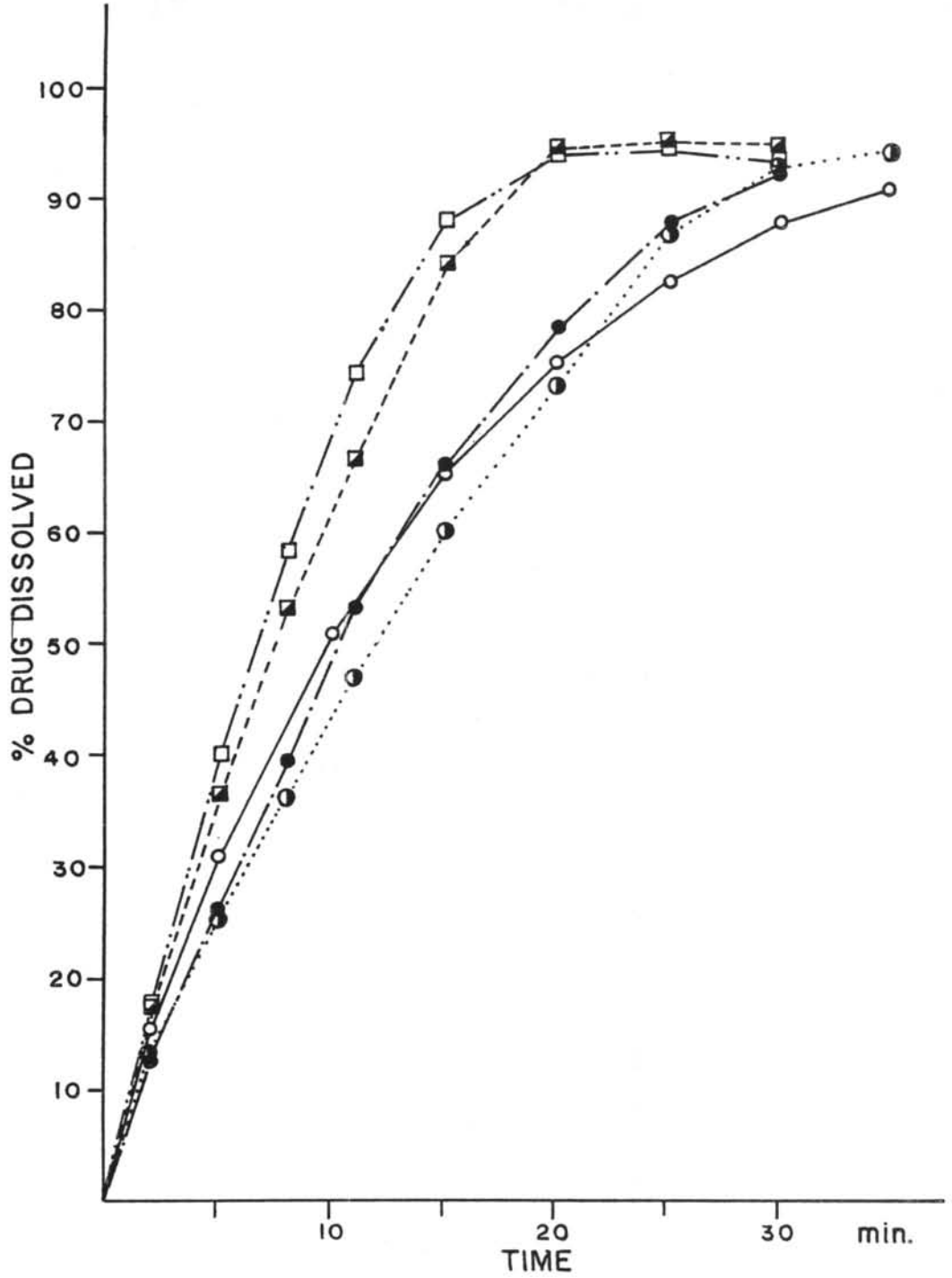

Figure 12 Dissolution Profiles of Dipyrone Tablets, Formula 26-30, Hardness 9-10 kg. (Each point on the curve is the mean value of 4 determinations.)

Key : —○— , Formula 26 (Non-disintegrant);

·····◑····· , Formula 27 (Corn Starch);

- - □ - - , Formula 28 (Sodium Alginate);

—·□·— , Formula 29 (Sodium Carboxymethylcellulose);

—·●·— , Formula 30 (Sodium Starch Glycolate).

except the disintegrants I and IV, II and III. Although, there was non-significant difference between the disintegrants II and III. The dissolution time of tablets containing disintegrant III was lower than the tablets containing disintegrant II. Therefore, at two levels of the hardness of tablets, the disintegrant III was considered satisfactory and found to be the best among four tablet disintegrants.

1.6.2 The Effects of Binding Agents on the Dissolution Time of Tablets

In consideration of the effects of binding agents on the dissolution time of tablets, the three different binding agents had been included in this study : corn starch paste, polyvinylpyrrolidone, and gelatin. When compared among the tablets containing corn starch as diluent and non-disintegrant, formulas 1, 6 and 11, the effects of binding agents on the dissolution time of tablets were ranked as follow : corn starch paste > gelatin > polyvinylpyrrolidone. The tablets when incorporated with the disintegrant III possessed the lowest dissolution time. Statistical analysis on the effects of binding agents on the dissolution time of tablets containing the disintegrant III, the results showed that there was significant at 5% level ($F_{2,9,0.05} = 4.26$, $F_{ratio} = 30.62$; tablet hardness 5-6 kg., $F_{ratio} = 492.49$; tablet hardness 9-10 kg.). While there was non-significant difference when compared between gelatin and polyvinylpyrrolidone by using Duncan's New Multiple Range Test. Therefore, polyvinylpyrrolidone and gelatin were considered satisfactory. But polyvinylpyrrolidone was more convenient than gelatin in the process

of preparation the solution and granules. So that, the polyvinylpyrrolidone was selected to be used as binding agent.

When compared among the tablets containing lactose as diluent and non-disintegrant, formulas 16, 21 and 26, the effects of binding agents on the dissolution time of tablets were ranked as follow : corn starch paste > gelatin > polyvinylpyrrolidone. When the tablets incorporated with the disintegrant III, the effects of three binding agents on the dissolution time of tablets were significant at 5% level ($F_{2,9,0.05} = 4.26$, $F_{ratio} = 175.33$; tablet hardness 5-6 kg., $F_{ratio} = 65.22$; tablet hardness 9-10 kg.). While there was non-significant difference when compared between gelatin and polyvinylpyrrolidone by using Duncan's New Multiple Range Test. Thus, polyvinylpyrrolidone and gelatin were considered satisfactory binding agents. But polyvinylpyrrolidone was more convenient than gelatin in the process of preparation the solution and granules. So that, the polyvinylpyrrolidone may be used as binding agent.

An increase in the hardness of tablets had a little change in the dissolution time of tablets granulating with polyvinylpyrrolidone and containing disintegrant III (Formulas 9 and 24).

1.6.3 The Effects of Diluents on the Dissolution Time of Tablets

When the disintegrant III and polyvinylpyrrolidone were selected to be used as disintegrant and binding agent. The comparison of the effects of diluents on the dissolution time of tablets was studied. Statistical analysis by using Unpair t-test,

Formulas 9 and 24, the results showed that there was non-significant difference between lactose and corn starch ($t_{6,0.05} = 2.447$, $\pm t_{observe} = -1.5465$; tablet hardness 5-6 kg., $\pm t_{observe} = -0.4979$; tablet hardness 9-10 kg.). Therefore, the corn starch or lactose may be used as diluent. But the corn starch was considered satisfactory because the cost of corn starch is lower than lactose.

On the basis of the dissolution time of tablets, it may be concluded as following :

The types of binding agents and disintegrating agents that used in the formulation of tablets had the different effects on the dissolution time of tablets. Sodium carboxymethylcellulose and sodium starch glycolate were considered satisfactory disintegrants. But sodium carboxymethylcellulose is better than sodium starch glycolate because the amount that recommended to use is lower[31,32]. Polyvinylpyrrolidone was better than gelatin when the tablets contained non-disintegrant. When the sodium carboxymethylcellulose was incorporated into tablets, there was non-significant difference between gelatin and polyvinylpyrrolidone. Corn starch and lactose had no different effects on the dissolution time of tablets.

Among 30 formulations of dipyrone tablets, the formulation of tablets containing corn starch as diluent, polyvinylpyrrolidone as binder, and sodium carboxymethylcellulose as disintegrant, Formula 9; tablet hardness 5-6 kg., possessed the lowest dissolution time (12.03 ± 1.35 minutes).

An increase in the hardness of tablets, the dissolution time of tablets increased.

2. Factorially Designed Experiment

2.1 The Effects of Additives

From the results of previous experiments, the following additives were selected to be used in the factorially designed experiment : corn starch as diluent, polyvinylpyrrolidone as binding agent, and sodium carboxymethylcellulose as disintegrating agent. The effects of additives on the dissolution time of tablets are shown in Table 10. The results of the analysis of variance are given in Table 11. In one-way interactions, only the effect of the corn starch is statistically significant. This result indicated that an increase in the amount of corn starch, the dissolution time of tablets decreased. In case of two-way interactions, the effects produced by the additives were found to be statistically non-significant.

2.2 The Effects of Lubricants

The formula E of dipyrone tablets was selected to be studied for this effect. The effects caused by magnesium stearate and talc were studied by factorially designed experiment as shown in Table 12. The results of the analysis of variance are given in Table 13. The effects produced by magnesium stearate and talc were found to be statistically non-significant.

The dissolution time of tablets showed that the combinations of lubricants employed have very little effect on the dissolution of

Table 10 The Effect of Additives on Dissolution Time of Dipyrone Tablet by Factorially Designed Experiment.

Variables : Corn Starch, Polyvinylpyrrolidone (PVP), Sodium Carboxymethylcellulose (Na CMC.)

Response : Dissolution Time, $t_{90\%}$, minute

Levels : Two : High and Low

				Corn Starch	
				Low (5%)	High (15%)
PVP	Low (10% Sol^{n})	Na CMC.	Low (1%)	12.34	8.78
			High (5%)	11.92	10.39
	High (20% Sol^{n})	Na CMC.	Low (1%)	9.33	8.58
			High (5%)	11.38	10.19

Table 11 Analysis of Variance of a Factorial.

One-way-interactions.

Variance of	D.F.	Sum of Squares	Variances	F-ratio
Corn Starch	1	6.1776	6.1776	8.0187*
PVP	1	1.9503	1.9503	2.5315
Na CMC.	1	2.9403	2.9403	3.8166
Error	4	3.0816	0.7704	
Total	7	14.1498		

*Critical F-value at the 5% level is 7.71

Two-way-interactions.

Variance of	D.F.	Sum of Squares	Variances	F-ratio
Corn Starch X PVP	2	4.3877	2.1938	0.2424
Corn Starch X Na CMC.	2	0.3065	0.1533	0.0169
PVP X Na CMC.	2	0.4066	0.2033	0.0225
Error	1	9.0490	9.0490	
Total	7	14.1498		

*Critical F-value at the 5% level is 200

Table 12 The Effect of Lubricants in Combination of Talc and Magnesium Stearate on Dissolution Time of Dipyrone Tablet by Factorially Designed Experiment.

Variables : Magnesium Stearate, Talc

Response : Dissolution Time, $t_{90\%}$, minute

Levels : Two : High and Low

		Talc	
		Low (3%)	High (5%)
Magnesium Stearate	Low (0.3%)	8.64	8.65
	High (1%)	8.78	9.05

Table 13 Analysis of Variance of a Factorial.

Variance of	D.F.	Sum of Squares	Variances	F-ratio
Magnesium Stearate	1	0.0729	0.0729	4.3136
Talc	1	0.0196	0.0196	1.1597
Error	1	0.0169	0.0169	
Total	3	0.1094		

*Critical F-value at the 5% level is 161.45

dipyrone from the tablets. There was no difference in the dissolution time of tablets containing the combination of magnesium stearate 0.3% with talc 1% and 5%. When the magnesium stearate 1% combined with talc 5% caused an increase in the dissolution time of tablets.

3. Properties of Dipyrone Tablets Containing Various Concentrations of Additives (Formula I to Formula XVIII)

The weight variation, percent labeled amount, hardness, friability, disintegration time and dissolution time ($t_{90\%}$) of dipyrone tablets are shown in Tables 21,22 and 23, respectively.

3.1 The Effect of Diluent

Corn Starch was used as diluent at the concentrations 5%, 10% and 15% of active ingredient. Formula I to IX, the tablets granulated with 10% W/W solution of polyvinylpyrrolidone. When compared among the tablets containing the same concentration of disintegrant, the results showed that the friability of tablets and the disintegration time of tablets increased when the concentrations of corn starch were increased. While the dissolution time of tablets decreased. By using Analysis of Variance (F-test) and Duncan's New Multiple Range Test, the effects of corn starch at the concentrations 10% and 15% of active ingredient had non-significant difference on the dissolution time of tablets.

Formula X to XVIII, the tablets granulated with 20% W/W solution of polyvinylpyrrolidone. When compared among the tablets containing the same concentration of disintegrant, the friability of tablets and the disintegration time of tablets increased when the concentra-

tions of corn starch were increased. The dissolution time of tablets increased when the concentration of corn starch was increased from 5% to 10%. But the increase of corn starch up to 15%, the dissolution time of tablets decreased. By using Analysis of Variance (F-test) and Duncan's New Multiple Range Test, the effect of corn starch at the concentration 15% of active ingredient had significant difference when compared with the other concentrations of corn starch.

3.2 The Effect of Binding Agent

Polyvinylpyrrolidone was used as binding agent and prepared to have the concentrations 10% W/W and 20% W/W solution. By comparing the effect of polyvinylpyrrolidone on the properties of tablets between the formulations of tablets containing the same concentration of disintegrant and diluent but granulating with the two different concentrations of polyvinylpyrrolidone solution, the friability of tablets granulating with 10% W/W solution of polyvinylpyrrolidone (I) was higher than the tablets granulating with 20% W/W solution of polyvinylpyrrolidone (II). The disintegration time of tablets granulating with I was lower than the tablets granulating with II. The dissolution time of tablets granulating with I was higher than the tablets granulating with II except the formulas V and XIV, VI and XV, VIII and XVII. By using Unpair t-test, the effect of two different concentrations of polyvinylpyrrolidone solution on the dissolution time of tablets had non-significant difference except the formulations of tablets containing 5% corn starch and 1% or 3% disintegrant.

3.3 The Effect of Disintegrating Agent

Sodium carboxymethylcellulose was used as disintegrating agent at the concentrations 1%, 3% and 5% of active ingredient. The disintegration time of tablets increased when the concentration of sodium carboxymethylcellulose was increased from 1% to 3% and 5%. By comparing among the formulations of tablets containing the same concentration of diluent and granulating with the same concentration of binder but incorporating with three different concentrations of sodium carboxymethylcellulose, the results showed that the dissolution time of tablets increased when the concentration of sodium carboxymethylcellulose was increased except the formulas I, II,and III. In the formulas I, II and III, the dissolution time of tablets increased when the concentration of sodium carboxymethylcellulose was increased from 1% to 3%. But from 3% to 5%, the dissolution time of tablets decreased and was lower than the tablets containing 1% sodium carboxymethylcellulose. Therefore, the sodium carboxymethylcellulose was found to be effective at a low concentration as 1% of active ingredient.